UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

BAYER SCHERING PHARMA AG and BAYER HEALTHCARE PHARMACEUTICALS INC.,

Plaintiffs,

v.

SANDOZ, INC.; WATSON PHARMACEUTICALS, INC.; and WATSON LABORATORIES, INC.

Defendants.

Case No. 2:08-cv-

COMPLAINT FOR PATENT INFRINGEMENT

JURY DEMAND

Plaintiffs Bayer Schering Pharma AG and Bayer HealthCare Pharmaceuticals Inc., for their Complaint for patent infringement herein against Defendants Sandoz, Inc.; Watson Pharmaceuticals, Inc.; and Watson Laboratories, Inc., allege as follows:

JURISDICTION AND VENUE

1. This action arises under the patent laws of the United States of America. This Court has jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331 and 1338(a).

2. Personal jurisdiction over the defendants in New York is proper under N.Y. C.P.L.R. §§ 301 and 302(a) and because defendants are, *inter alia*, doing business in this jurisdiction and have submitted to the jurisdiction of the Courts in New York by registering with the New York Department of State, Division of Corporations.

3. Venue is proper in this judicial district under 28 U.S.C. § 1391(b) and (c), and § 1400(b).

PARTIES

4. Plaintiff Bayer Schering Pharma AG ("Bayer Schering"), formerly known as Schering AG, is a corporation organized and existing under the laws of the Federal Republic of Germany, having a principal place of business at Müllerstrasse 178, 13353 Berlin, Germany.

5. Plaintiff Bayer HealthCare Pharmaceuticals Inc. ("Bayer HealthCare"), formerly known as Berlex, Inc., is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 340 Changebridge Road, P.O. Box 1000, Montville, New Jersey 07045-1000.

6. On information and belief, Defendant Sandoz, Inc. ("Sandoz") is a corporation organized and existing under the laws of the State of Colorado, having a principal place of business at 506 Carnegie Center, Suite 400, Princeton, New Jersey 08540. Defendant Sandoz develops, manufactures and markets generic pharmaceutical products.

7. On information and belief, Sandoz is currently transacting business in the State of New York, at least by making and shipping into this State, or by using, offering to sell or selling, or by causing others to use, offer to sell or sell, pharmaceutical products. On information and belief, Sandoz also operates a manufacturing facility in this State, which is located in Laurelton, New York. On information and belief, Sandoz derives substantial revenue from interstate and/or international commerce, including substantial revenue from goods used or consumed or services rendered in the State of New York and this Judicial District. By filing its Abbreviated New Drug Application ("ANDA"), Sandoz has committed, and unless enjoined, will continue to commit a tortious act without the state of New York, which Sandoz expects or should reasonably expect to have consequences in the State of New York. In addition, Sandoz is registered with the New York Department of State, Division of Corporations, to do business as a foreign corporation in New York.

8. On information and belief, Defendant Watson Pharmaceuticals, Inc. is a corporation organized and existing under the laws of the State of Nevada, having a principal place of business at 311 Bonnie Circle, Corona, California 92880. Defendant Watson Pharmaceuticals, Inc. develops, manufactures and markets generic pharmaceutical products through its operating subsidiary Defendant Watson Laboratories, Inc.

9. On information and belief, Defendant Watson Laboratories, Inc. is a corporation organized and existing under the laws of, *inter alia*, the States of New York and Nevada, having a principal place of business at 311 Bonnie Circle, Corona, California 92880. By virtue of its incorporation under the laws of the State of New York, Defendant Watson Laboratories, Inc. is a resident of this State.

10. On information and belief, Watson Laboratories, Inc. operates manufacturing and distribution facilities in this State. On information and belief, Watson Laboratories, Inc. derives substantial revenue from interstate and/or international commerce, including substantial revenue from goods used or consumed or services rendered in the State of New York and this Judicial District. On information and belief, Watson Laboratories, Inc. is listed in the United States Food and Drug Administration's ("FDA's") National Drug Code Directory with a New York State contact address.

11. By filing its ANDA, Watson has committed, and unless enjoined, will continue to commit a tortious act without the state of New York, which Watson expects or should reasonably expect to have consequences in the State of New York.

12. On information and belief, Defendant Watson Laboratories, Inc. is a wholly-owned subsidiary of Defendant Watson Pharmaceuticals, Inc., and the two have common officers and directors.

13. On information and belief, Defendant Watson Pharmaceuticals, Inc. directed, authorized, participated in, assisted and cooperated with Defendant Watson Laboratories, Inc. in all of the acts complained of herein. Hereinafter, Defendants Watson Pharmaceuticals, Inc. and Watson Laboratories, Inc. are collectively referred to as "Watson."

14. Upon information and belief, Watson is currently transacting business in the State of New York, at least by making and shipping into this State, or by using, offering to sell or selling, or by causing others to use, offer to sell or sell, pharmaceutical products. Upon information and belief, Watson derives substantial revenue from interstate and/or international commerce, including substantial revenue from goods used or consumed or services rendered in the State of New York and this Judicial District. By filing its ANDA, Watson has committed, and unless enjoined, will continue to commit a tortious act without the state of New York, which Watson expects or should reasonably expect to have consequences in the State of New York.

BACKGROUND

15. Bayer HealthCare is the holder of approved New Drug Application ("NDA") No. 21-676, for YAZ® tablets, which contain as active ingredients micronized drospirenone and micronized 17α -ethinylestradiol. YAZ® tablets have been approved by the FDA for (a) the prevention of pregnancy in women who elect to use an oral contraceptive; (b) the treatment of acne; and (c) premenstrual dysphoric disorder ("PMDD"). YAZ® tablets are sold in the United States by Bayer HealthCare as a 28-day oral contraceptive regimen that contains 24 tablets comprising 3 mg of micronized drospirenone and 0.02 mg of micronized 17α -ethinylestradiol plus 4 placebo tablets.

16. On information and belief, Sandoz submitted to the FDA an ANDA under the provisions of 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture,

use, offer for sale, sale and/or importation of a generic version of Bayer HealthCare's YAZ® tablets. On information and belief, the FDA has assigned this Sandoz ANDA the number 79-221.

17. On information and belief, the composition of the product that is the subject of Sandoz's ANDA contains 3 mg of drospirenone and 0.02 mg of 17α -ethinylestradiol in tablet form for oral contraception in a human female.

18. On information and belief, Sandoz's ANDA seeks approval of a 28-day oral contraceptive regimen that contains 24 tablets comprising 3 mg drospirenone and 0.02 mg 17α –ethinylestradiol plus 4 placebo tablets (hereinafter, "Sandoz's ANDA product").

19. On information and belief, on or about June 19, 2008, Sandoz sent a Notice Letter to Plaintiffs Bayer Schering and Bayer HealthCare, purporting to comply with the provisions of 21 U.S.C. § 355(j)(2)(B) and the FDA regulations relating thereto.

20. On information and belief, Watson submitted to the FDA an ANDA under the provisions of 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use, offer for sale, sale and/or importation of a generic version of Bayer HealthCare's YAZ® tablets. On information and belief, the FDA has assigned this Watson ANDA the number 78-833.

21. On information and belief, the composition of the product that is the subject of Watson's ANDA contains 3 mg of drospirenone and 0.02 mg of 17α –ethinylestradiol in tablet form for oral contraception in a human female.

22. On information and belief, Watson's ANDA seeks approval of a 28-day oral contraceptive regimen that contains 24 tablets comprising 3 mg drospirenone and 0.02 mg 17α –ethinylestradiol plus 4 placebo tablets (hereinafter "Watson's ANDA product").

23. On information and belief, on or about October 1, 2007, Watson sent a Notice Letter to Plaintiffs Bayer Schering and Bayer HealthCare, purporting to comply with the provisions of 21 U.S.C. § 355(j)(2)(B) and the FDA regulations relating thereto.

PATENT-IN-SUIT

24. The patent-in-suit is United States Patent No. 5,569,652 ("the '652 patent") (attached as Exhibit 1). Inventors Sybille Beier, Walter Elger, Yukishige Nishino, and Rudolf Wiechert filed their application for this patent on December 7, 1993. The '652 patent issued on October 29, 1996. Bayer Schering is the current owner of the '652 patent.

25. The '652 patent covers certain uses of Bayer HealthCare's YAZ® tablets and has been listed for the product in the FDA's publication, *Approved Drug Products with Therapeutic Equivalence Evaluations* ("the Orange Book").

COUNT ONE: CLAIM FOR PATENT INFRINGEMENT OF UNITED STATES PATENT NO. 5,569,652 AGAINST SANDOZ, INC. UNDER 35 U.S.C. §271(E)(2)(A)

26. Plaintiffs incorporate each of the preceding paragraphs of this Complaint as if fully set forth herein.

27. Sandoz's filing of ANDA 79-221 for the purpose of obtaining FDA approval to engage in the commercial manufacture, use, importation, offer for sale and/or sale, or inducement thereof, of drug products containing drospirenone and ethinylestradiol before the expiration of the '652 patent is an act of infringement under 35 U.S.C. § 271(e)(2)(A).

28. Sandoz's manufacture, use, importation, offer for sale, and/or sale, or inducement thereof, of its proposed drospirenone and ethinylestradiol drug product will induce infringement of at least one claim of the '652 patent under 35 U.S.C. § 271(e)(2)(A).

29. Upon information and belief, Sandoz is aware, or reasonably should be aware, of the widespread use of YAZ® (drospirenone and ethinylestradiol) to produce simultaneously a gestagenic, anti-androgenic, and anti-aldosterone effect in premenopausal or menopausal female patients. This use of drospirenone and ethinylestradiol to produce simultaneously these three effects would be readily apparent to customers of Sandoz (*e.g.*, including, without limitation, physicians, pharmacists, pharmacy benefits management companies, health care providers who establish drug formularies for their insurers and/or patients). Further, by filing its ANDA, Sandoz has indicated that its ANDA product will be bioequivalent to Plaintiffs' YAZ® product.

30. Upon information and belief, Sandoz's proposed label for its drospirenone and ethinylestradiol product does not restrict the intended use of its product to the creation of a gestagenic effect in patients. As is well known to Sandoz, a significant proportion of drospirenone and ethinylestradiol prescriptions are written with the intent of producing three pharmacological effects — gestagenic, anti-aldosterone, and anti-androgenic. The beneficial effects of simultaneously and intentionally producing these three effects are well known to Sandoz and customers of Sandoz. On information and belief, Sandoz will be marketing its ANDA product with specific intent, and/or with the desire to actively induce, aid, and abet infringement of the '652 patent. Sandoz knows or reasonably should know that its proposed conduct will induce infringement.

31. Upon information and belief, Sandoz's proposed label provides or will be required by the FDA to provide, information for patients regarding the anti-aldosterone and anti-androgenic properties of drospirenone. By including this information in its proposed label, Sandoz will be marketing its ANDA product with specific intent, and/or with the desire to actively induce, aid, and abet infringement of the '652 patent. Sandoz knows or reasonably should know that its proposed conduct will induce infringement.

32. Drospirenone's pharmacological profile — *i.e.* its three mechanisms of action gestagen, anti-aldosterone, and anti-mineralocorticoid — is disclosed in the approved product insert for YAZ®. The use of drospirenone under conditions where drospirenone will exhibit this pharmacological profile is thus within the scope of the approved product insert.

33. Upon information and belief, Sandoz's generic marketing practices include listing generic products on its website and referring customers (*e.g.*, including, without limitation, physicians, pharmacists, pharmacy benefits management companies, health care providers who establish drug formularies for their insurers and/or patients) to a corresponding brand name product. Upon information and belief, Sandoz intends to do the same for any approved generic drospirenone and ethinylestradiol product with respect to Bayer HealthCare's YAZ® tablets.

34. Upon information and belief, Sandoz's generic marketing practices include representing to its customers (*e.g.*, including, without limitation, physicians, pharmacists, pharmacy benefits management companies, health care providers who establish drug formularies for their insurers and/or patients) that its generic products are bioequivalent to a corresponding brand name product and therefore representing (implicitly or explicitly or both) that Sandoz's generic products are suitable for the same pharmacological uses as the corresponding branded product. Upon information and belief, Sandoz intends to do the same for any approved drospirenone and ethinylestradiol product with respect to Bayer HealthCare's YAZ® tablets.

35. Upon information and belief, Sandoz has planned and intended to actively induce others to infringe the '652 patent when its ANDA application is approved and plans and intends to do so on approval.

36. Unless Sandoz is enjoined from infringing and inducing the infringement of the '652 patent, Plaintiffs will suffer substantial and irreparable injury. Plaintiffs have no adequate remedy at law.

COUNT TWO: CLAIM FOR PATENT INFRINGEMENT OF UNITED STATES PATENT NO. 5,569,652 AGAINST SANDOZ, INC. UNDER 35 U.S.C. §271(B)

37. Plaintiffs incorporate each of the preceding paragraphs of this Complaint as if fully set forth herein.

38. Upon information and belief, approval of ANDA 79-221 is substantially likely to result in the commercial manufacture, use, importation, offer for sale, and/or sale, or inducement thereof, of a drug product which is marketed and sold for use in a method claimed in one or more claims of the '652 patent, immediately or imminently upon approval of the ANDA.

39. Unless Sandoz is enjoined from infringing and inducing the infringement of the '652 patent, Plaintiffs will suffer substantial and irreparable injury. Plaintiffs have no adequate remedy at law.

COUNT THREE: CLAIM FOR PATENT INFRINGEMENT OF UNITED STATES PATENT NO. 5,569,652 AGAINST WATSON UNDER 35 U.S.C. §271(E)(2)(A)

40. Plaintiffs incorporate each of the preceding paragraphs of this Complaint as if fully set forth herein.

41. Watson's filing of ANDA 78-833 for the purpose of obtaining FDA approval to engage in the commercial manufacture, use, importation, offer for sale and/or sale, or inducement thereof, of drug products containing drospirenone and ethinylestradiol before the expiration of the '652 patent is an act of infringement under 35 U.S.C. § 271(e)(2)(A).

42. Watson's manufacture, use, importation, offer for sale, and/or sale, or inducement thereof, of its proposed drospirenone and ethinylestradiol drug product will induce infringement of at least one claim of the '652 patent under 35 U.S.C. § 271(e)(2)(A).

43. Upon information and belief, Watson is aware, or reasonably should be aware, of the widespread use of YAZ® (drospirenone and ethinylestradiol) to produce simultaneously a

gestagenic, anti-androgenic, and anti-aldosterone effect in premenopausal or menopausal female patients. This use of drospirenone and ethinylestradiol to produce simultaneously these three effects would be readily apparent to customers of Watson (*e.g.*, including, without limitation, physicians, pharmacists, pharmacy benefits management companies, health care providers who establish drug formularies for their insurers and/or patients). Further, by filing its ANDA, Watson has indicated that its ANDA product will be bioequivalent to Plaintiffs' YAZ® product.

44. Upon information and belief, Watson's proposed label for its drospirenone and ethinylestradiol product does not restrict the intended use of its product to the creation of a gestagenic effect in patients. As is well known to Watson, a significant proportion of drospirenone and ethinylestradiol prescriptions are written with the intent of producing three pharmacological effects — gestagenic, anti-aldosterone, and anti-androgenic. The beneficial effects of simultaneously and intentionally producing these three effects are well known to Watson and customers of Watson. On information and belief, Watson will be marketing its ANDA product with specific intent, and/or with the desire to actively induce, aid, and abet infringement of the '652 patent. Watson knows or reasonably should know that its proposed conduct will induce infringement.

45. Upon information and belief, Watson's proposed label provides or will be required by the FDA to provide, information for patients regarding the anti-aldosterone and anti-androgenic properties of drospirenone. By including this information in its proposed label, Watson will be marketing its ANDA product with specific intent, and/or with the desire to actively induce, aid, and abet infringement of the '652 patent. Watson knows or reasonably should know that its proposed conduct will induce infringement.

46. Drospirenone's pharmacological profile — *i.e.* its three mechanisms of action gestagen, anti-aldosterone, and anti-mineralocorticoid — is disclosed in the approved product

insert for YAZ®. The use of drospirenone under conditions where drospirenone will exhibit this pharmacological profile is thus within the scope of the approved product insert.

47. Upon information and belief, Watson's generic marketing practices include listing generic products on its website and referring customers (*e.g.*, including, without limitation, physicians, pharmacists, pharmacy benefits management companies, health care providers who establish drug formularies for their insurers and/or patients) to a corresponding brand name product. Upon information and belief, Watson intends to do the same for any approved generic drospirenone and ethinylestradiol product with respect to Bayer HealthCare's YAZ® tablets.

48. Upon information and belief, Watson's generic marketing practices include representing to its customers (*e.g.*, including, without limitation, physicians, pharmacists, pharmacy benefits management companies, health care providers who establish drug formularies for their insurers and/or patients) that its generic products are bioequivalent to a corresponding brand name product and therefore representing (implicitly or explicitly or both) that Watson's generic products are suitable for the same pharmacological uses as the corresponding branded product. Upon information and belief, Watson intends to do the same for any approved drospirenone and ethinylestradiol product with respect to Bayer HealthCare's YAZ® tablets.

49. Upon information and belief, Watson has planned and intended to actively induce others to infringe the '652 patent when its ANDA application is approved and plans and intends to do so on approval.

50. Unless Watson is enjoined from infringing and inducing the infringement of the '652 patent, Plaintiffs will suffer substantial and irreparable injury. Plaintiffs have no adequate remedy at law.

COUNT FOUR: CLAIM FOR PATENT INFRINGEMENT OF UNITED STATES PATENT NO. 5,569,652 AGAINST WATSON UNDER 35 U.S.C. §271(B)

51. Plaintiffs incorporate each of the preceding paragraphs of this Complaint as if fully set forth herein.

52. Upon information and belief, approval of ANDA 78-833 is substantially likely to result in the commercial manufacture, use, importation, offer for sale, and/or sale, or inducement thereof, of a drug product which is marketed and sold for use in a method claimed in one or more claims of the '652 patent, immediately or imminently upon approval of the ANDA.

53. Unless Watson is enjoined from infringing and inducing the infringement of the '652 patent, Plaintiffs will suffer substantial and irreparable injury. Plaintiffs have no adequate remedy at law.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request the following relief:

A. A declaratory judgment pursuant to 28 U.S.C. § 2201 et seq. that making, using, selling, offering to sell and/or importing Defendants' respective generic drug products containing drospirenone and ethinylestradiol for which Defendants seek FDA approval will infringe at least one claim of the '652 patent;

B. A declaratory judgment pursuant to 28 U.S.C. § 2201 et seq. that inducing the making, using, offering for sale, selling and/or importing of Defendants' respective generic drug products containing drospirenone and ethinylestradiol, will infringe at least one claim of the '652 patent;

C. A declaratory judgment pursuant to 28 U.S.C. § 2201 et seq. and an order pursuant to 35 U.S.C. § 271(e)(4)(A) providing that the effective date of any FDA approval for

Defendants to commercially make, use, sell, offer to sell or import their respective generic drug products containing drospirenone and ethinylestradiol be no earlier than the date following the expiration date of the '652 patent (as extended, if applicable);

D. A permanent injunction restraining and enjoining Defendants and their officers, agents, attorneys and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of their respective generic products containing drospirenone and ethinylestradiol;

E. Such other and further relief as the Court may deem just and proper.

JURY DEMAND

Plaintiffs hereby demand a jury trial on all issues so triable.

DATED: this 18th day of September, 2008.

By: _____

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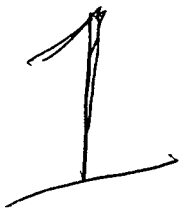

US005569652A

United States Patent [19]

Beier et al.

[11] **Patent Number: 5,569,652**

[45] **Date of Patent: Oct. 29, 1996**

[54] **DIHYDROSPIRORENONE AS AN ANTIANDROGEN**

[75] Inventors: **Sybille Beier; Walter Elger; Yukishige Nishino; Rudolf Wiechert**, all of Berlin, Germany

[73] Assignee: **Schering Aktiengesellschaft**, Berlin, Germany

[21] Appl. No.: **162,387**

[22] Filed: **Dec. 7, 1993**

Related U.S. Application Data

[63] Continuation of Ser. No. 835,000, Feb. 14, 1992, abandoned, which is a continuation of Ser. No. 524,396, May 16, 1990.

[30] **Foreign Application Priority Data**

May 16, 1989 [DE] Germany 39 16 112.9

[51] **Int. Cl.**[6] **A61K 31/585**

[52] **U.S. Cl.** **514/173**; 514/172

[58] **Field of Search** 514/173, 172; 540/11, 8

[56] **References Cited**

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4,502,989	3/1985	Kamata et al.	552/615
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4,729,999	3/1988	Young	514/227
4,855,289	8/1989	Wester et al.	514/171
4,868,166	9/1989	Bittler et al.	514/173

FOREIGN PATENT DOCUMENTS

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2652 761 5/1978 Germany .

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Nishino et al., Arch Pharmacol., vol. 316, R49 (1981).

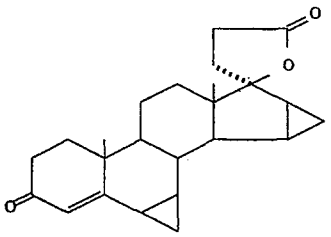
Nishino et al., Acta Endocrinologica, Suppl. 246, vol. 99, p. 93, Abstract 105 (1982).

Primary Examiner—Theodore J. Criares

Attorney, Agent, or Firm—Millen, White, Zelano, & Branigan, P.C.

[57] **ABSTRACT**

Dihydrospirorenone,



(I)

preferably together with an estrogen, can be used for the production of a pharmaceutical agent suitable for treatment of hormonal irregularities during premenopause (menstruation stabilization), for hormonal substitution therapy during menopause, for treatment of androgen-induced disorders and/or for contraception.

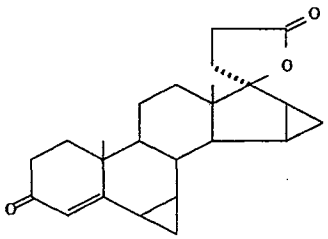
27 Claims, No Drawings

DIHYDROSPIRORENONE AS AN ANTIANDROGEN

This application is a continuation of application Ser. No. 07/835,000, filed Feb. 14, 1992, ABN, which is a continuation of Ser. No. 07/524,396, filed May 16, 1990.

BACKGROUND OF THE INVENTION

This invention relates to the use of the compound of formula I



(I)

for the production of a pharmaceutical agent.

Compound I (dihydrospirorenone) is described in DE A-26 52 761, among others, as a diuretic of the aldosterone-antagonist type.

It can be seen from DE-A 30 22 337 that compound I, at doses at which the antialdosterone effect already appears, also exhibits a marked gestagen effect. Therefore, compound I can be used alone or in combination with estrogens in contraceptive preparations.

According to DE-A 30 22 337, these preparations are to be used for women who desire contraception and suffer from high blood pressure or in whom blood pressure rises when they take oral contraceptives. Thus, also for women predisposed to increased blood pressure, hormonal contraception is possible.

A combined preparation for substitution therapy and contraception for women before menopause (starting at about age 40) is known from EP-A 0253 607. This combined preparation contains an estrogen from the group

17beta-estradiol,

ethynylestradiol and

mestranol

and a gestagen from the group

levonorgestrel,

gestodene,

desogestrel,

3 ketodesogestrel and

norethindrone.

A composition so selected should balance hormonal irregularities in the transition phase of premenopause and help to alleviate the discomfort caused by the hormonal change of the female organism during this phase. Simultaneously, such a composition guarantees the contraceptive protection still necessary at this age.

For various, known reasons and because of the increase in the incidence of contraindications with increasing age, the taking of the usual hormonal contraceptives is recommended for women only until about age 35, so that a hormonal treatment during premenopause and a substitution therapy during menopause using doses that simultaneously have a contraceptive effect can be considered problematic.

Besides these circumstances justifying contraindication, in women of such advanced age, symptoms of androgenization such as, for example, beard growth, deepening of the voice and impure skin are often observed; further, a rise in blood pressure can often be noted.

Thus, there remains a need for good agents for hormonal therapy, especially for such woman, including achievement of one or more of such effects.

SUMMARY OF THE INVENTION

It has now been found that the compound of formula I, in addition to its gestagen and antialdosterone effect, surprisingly exhibits a strong antiandrogenic activity component, and specifically at doses that also make possible the formulation of this compound as an oral contraceptive. Dihydrospirorenone acts as an antiandrogen about as strongly as cyproterone acetate, considered the standard compound (same maximum effect). (Animal model: juvenile, castrated and testosterone-substituted male rat.)

This invention thus relates to the use of the compound of formula I for the production of a pharmaceutical agent suitable for treatment of hormonal irregularities during premenopause (e.g., menstruation stabilization) and/or for hormonal substitution therapy during menopause and/or for treatment of androgen-induced disorders and/or for contraception. Conventional protocols can be used to determine antiandrogenic activity, e.g., as disclosed in Methods in Hormone Research, Editor: R. I. Dorfman, Academic Press, New York, London, 1969, pp. 241; or Androgens and Antiandrogens, Editors: L. Martin and M. Motta, Raven Press, New York, 1977, pp. 163.

Thus, in various aspects, this invention relates to a method of achieving an antiandrogenic effect comprising administering I to a patient in need of antiandrogenic treatment; to a method of treating an androgen induced disorder in a female comprising administering I; to a method of achieving a contraceptive effect in a female during premenopause or menopause (both terms having their conventional meaning, e.g., as shown in "The Controversial Climacteric," P. A. van Keep et al., Ed., MTP Press (1981), e.g., page 9) comprising administering to the female an effective amount of I; to a method of treating gestagen-related hormonal irregularities in a female during premenopause comprising administering I; and/or to a method of achieving gestogen-related hormonal substitution therapy in a female in menopause comprising administering I. In preferred aspects, the females are suffering from and/or predisposed to high blood pressure disorders and/or to androgen-related disorders.

Preferably an estrogen is used together with the compound of formula I. Whether a synthetic or a natural estrogen is preferably used depends on whether the contraceptive effect or the substitutive effect is emphasized: in the first case, ethynylestradiol or another synthetic estrogen is preferred, in the second case, such a pharmaceutical agent should contain a natural estrogen.

But in any case, such a pharmaceutical agent guarantees a woman of middle age (about age 35–55) a stabilization of her menstruation cycle and the contraception still indispensable at this age, with simultaneous, favorable influence on androgen-induced disorders. Of course, this pharmaceutical agent is also suited for younger women, especially for those that have a particular predisposition toward high blood pressure and/or suffer from symptoms of androgenization or are predisposed to one or both of these, e.g., in view of their past medical history, family background, etc., in addition to age.

Here such a use is especially effective because the compound of formula I simultaneously combines a gestagen,

antialdosterone effect as well as a strong antiandrogen effect. Previously no substance was known that simultaneously exhibited these three properties.

The dose of the compound of formula I can be 0.5 to 50 mg per day, preferably 1–10 mg per day for all uses of this invention.

Suitable as estrogens are all previously known estrogens. The estrogen used preferably for the various purposes of this invention should be administered in doses such that the estrogen amount used according to the invention is equal to that which corresponds to the administration of 0.02 to 0.04 mg of 17alpha-ethynylestradiol or 0.5 to 4.0 mg of estradiol valerate daily. Such amounts can be conventionally determined using fully conventional tests such as described in Dorfman, supra, page 62. As estrogenic components, among others the 17alpha-ethynyl-estradiol esters and ethers are suitable as well as, for example, esters of 17alpha-ethynyl-7alpha-methyl-1,3,5(10)-estratriene-1,3,17beta-triol (German patent 1 593 509 and German laid-open specification 2 818 164). Further, also the 14,17beta-ethano-14beta-estratrienes described in DE-A 36 28 189 as useful. The estrogenic and gestagenic active components are preferably administered together orally: but they can also be administered separately and/or parenterally or transdermally.

The agents of this invention can be used in the methods of this invention analogously to use of agents known for such purposes, e.g., those of EP 253607 but routinely taking into account the beneficial properties discussed herein.

The formulation of the preparations according to the invention based on 6beta, 7beta; 15beta, 16beta-dimethylene- 3-oxo-4-androstene-[17(beta-1']-perhydrofuran-2'-one (I) is performed in a way known in the art by processing the active ingredient, optionally in combination with an estrogen, with the vehicles, diluents, optional flavorings, etc. common in galenicals, and converting it into the desired form of administration. For the preferred oral administration, tablets, coated tablets, capsules, pills, suspensions or solutions are especially suitable. For parenteral administration, in particular oily solutions, such as, for example, solutions in sesame oil, castor oil and cottonseed oil, are suitable. To increase solubility, solubilizers such as, for example, benzyl benzoate or benzyl alcohol, can be added.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

In the foregoing and in the following examples, all temperatures are set forth uncorrected in degrees Celsius and unless otherwise indicated, all parts and percentages are by weight.

The entire disclosures of all applications, patents and publications, if any, cited above and below, and of corresponding application Federal Republic of Germany P 39 16 112.9, filed May 16, 1989, are hereby incorporated by reference.

EXAMPLES

Example 1

20.0 mg of 6beta, 7beta; 15beta, 16beta-dimethylene-3-oxo-4-androstene-[17(beta-1')-spiro-5']-perhydrofuran-2'-one and 0.05 mg of 17alpha-ethynylestradiol are mixed homogeneously with 140.45 mg of lactose, 59.5 mg of cornstarch, 2.0 mg of aerosil, 2.5 mg of polyvinylpyrrolidone 25 and 0.5 mg of magnesium stearate and pressed without advance granulation into a tablet of 225 mg final weight.

Example 2

Analogous to example 1, 10 mg of 6beta, 7beta; 15beta, 16beta-dimethylene-3-oxo-4-androstene-[17(beta-1')-spiro-5']-perhydrofuran-2'-one and 0.05 mg of 17alpha-ethynylestradiol with 150.45 mg of 17alpha-ethynylestradiol with 150.45 mg of lactose, 59.5 mg of cornstarch, 2.0 mg of aerosil, 2.5 mg of polyvinylpyrrolidone 25 and 0.5 mg of magnesium stearate are pressed into tablets with a final weight of 225 mg.

Example 3

Analogous to example 1, 20 mg of 6beta, 7beta; 15beta, 16beta-dimethylene-3-oxo-4-androstene-[17(beta-1')-spiro-5']-perhydrofuran-2'-one with 140.5 mg of lactose, 59.5 mg of cornstarch, 2.0 mg of aerosil, 2.5 mg of polyvinylpyrrolidone 25 and 0.5 mg of magnesium stearate are pressed into tablets with a final weight of 225 mg.

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

What is claimed is:

1. A method of simultaneously achieving, during premenopause or menopause a gestagenic effect, antiandrogenic effect, and an antialdosterone effect in a female patient in need thereof comprising administering an amount of dihydrospirorenone to said female patient, wherein said amount of dihydrospirorenone is effective to simultaneously achieve a gestagenic effect, antiandrogenic effect and antialdosterone effect in said patient.

2. A method according to claim **1**, wherein said patient is in premenopause.

3. A method of claim **2**, wherein stabilization of menstruation is achieved.

4. A method according to claim **1**, wherein said female is of age 35–55.

5. A method according to claim **1**, wherein said patient is in menopause.

6. A method according to claim **1**, wherein said effective amount of dihydrospirorenone is 0.5–50 mg per day.

7. A method according to claim **6**, wherein said effective amount of dihydrospirorenone is 1–10 mg per day.

8. A method of claim **1**, wherein said patient is predisposed to androgenization symptoms.

9. A method of claim **1**, wherein said patient suffers from or is predisposed to high blood pressure.

10. A method of claim **2**, wherein said patient suffers from or is predisposed to high blood pressure.

11. A method of simultaneously achieving, during premenopause or menopause, a contraceptive effect, an antiandrogenic effect, and an anti-aldosterone effect in a female patient in need thereof comprising administering an effective amount of dihydrospirorenone and an effective amount of an estrogenic compound, wherein said effective amount of dihydrospirorenone is effective to simultaneously achieve a

gestagenic effect, anti-androgenic effect, and an anti-aldosterone effect in said female patient.

12. A method according to claim **11**, wherein said effective amount of dihydrospirorenone is 0.5–50 mg per day and said effective amount of an estrogenic compound is an amount equivalent to 0.5–4.0 mg of estradiol valerate per day.

13. A method of claim **11**, wherein said patient suffers from symptoms of androgenization.

14. A method of claim **11**, wherein said patient suffers from or is predisposed to high blood pressure.

15. A method of claim **13**, wherein said patient is in premenopause.

16. A method of claim **13**, wherein said patient suffers from or is predisposed to high blood pressure.

17. A method of claim **11**, wherein said estrogenic compound is a synthetic estrogen.

18. A method of claim **11**, wherein said estrogenic compound is a natural estrogen.

19. A method according to claim **11**, wherein said female is of age 35–55.

20. A method of claim **11**, wherein said estrogenic compound is a synthetic estrogen.

21. A method of claim **12**, wherein said estrogenic compound is a natural estrogen.

22. A method of claim **11**, wherein the estrogenic compound is 17α-ethynylestradiol.

23. A method of claim **11**, wherein said patient is in menopause.

24. A method according to claim **11**, wherein said effective amount of dihydrospirorenone is 1–10 mg per day.

25. A method of claim **11**, wherein said patient is predisposed to androgenization symptoms.

26. A method of claim **15**, wherein stabilization of menstruation is achieved.

27. A method according to claim **11**, wherein said effective amount of dihydrospirorenone is 0.5–50 mg per day and said effective amount of an estrogenic compound is an amount equivalent to 0.02–0.04 mg of 17α-ethynylestradiol per day.

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